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30. (Twice amended) An isolated cell containing a tissue-specific replication-conditional adenovirus virion, said virion comprising

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a heterologous tissue-specific transcriptional regulatory sequence operably linked to the coding region of a gene that is essential for replication of said virion, wherein said transcriptional regulatory sequence functions in said cell so that replication of the virion occurs in said cell, wherein said coding region is selected from the group consisting of E1a, E1b, and E2 and E4 coding regions.

Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-3, 8, 19-22, 27-33, 38-40, 43 and 44 are pending in the application, with claims 1, 19 and 30 being the independent claims.

Entry of the amendment after final rejection is respectfully requested. The present amendment is to cancel claims 7, 9-12, 16-18, 26, 37, 41 and 42 and to add the limitations of canceled claims 7, 26 and 37 to claims 1, 19 and 30, respectively. Since the subject matter of canceled claims 7, 26 and 37 has already been considered by the Examiner, entry of the amendment will not require additional searching or consideration of the amendment. Entry of the amendment does not enter any new matter and will simplify the issues for allowance or appeal. These amendments are presented in accordance with the telephone interviews with the Examiner held May 12 and 13, 1999, where the outstanding rejections were discussed. Therefore, entry of the amendment after final rejection is appropriate.

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Description of the Invention

The invention as claimed relates generally to recombinant vectors, particularly recombinant adenovirus vectors. The invention as claimed relates more specifically to replication-conditional adenovirus vectors, particularly such vectors that undergo tissue-specific replication. The vectors of the invention comprise a heterologous tissue-specific transcriptional regulatory sequence operably linked to the coding region of a gene that is essential for replication of the vectors, i.e. E1a, E1b, and E2 and E4 coding regions. The invention as claimed also relates to isolated cells, particularly cell lines, containing such replication-conditional adenovirus vectors. The present invention thus provides compositions and methods, not previously available in the art, that may be used for a variety of clinical and diagnostic purposes.

Rejections under 35 U.S.C. § 112

The Examiner has maintained the rejection of claims 9-12 and 16-18 under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not provide enablement for claims drawn to methods for distributing a polynucleotide in any tissue *in vivo*. Applicants respectfully traverse this rejection.

Applicants reiterate and incorporate by reference the remarks presented in the Amendment and Reply under 37 C.F.R. § 1.111 filed October 13, 1998. The specification fully enables the practice of the invention defined by claims 9-12 and 16-18.

Solely to advance the prosecution of the present application, Applicants have canceled claims 9-12 and 16-18. Withdrawal of the rejection is respectfully requested.

The Examiner has maintained the rejection of claims 9-12 and 16-18 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. In particular, the Examiner states that the claims are indefinite:

> in the recitation of the phrase "distributing a polynucleotide in a tissue *in vivo*" because it is not apparent as to what are the metes and bounds of the distribution of a polynucleotide *in vivo* in accomplishing a therapeutic effect. Furthermore, claim 17 is indefinite because it is not apparent as to what is the stated effect of *in vivo* gene expression of a heterologous gene in accomplishing a beneficial effect.

Paper no. 12, page 5, lines 11-15.

Applicants respectfully traverse this rejection. Applicants reiterate and incorporate by reference the remarks presented in the Amendment and Reply under 37 C.F.R. § 1.111 filed October 13, 1998. Claims 9-12 and 16-18 are definite under 35 U.S.C. § 112, second paragraph.

Solely to advance the prosecution of the present application, Applicants have canceled claims 9-12 and 16-18. Withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. § 103

The Examiner has rejected claims 1-5, 8-14, 17-24, 27-35 and 38-40 under 35 U.S.C. § 103(a) as being unpatentable over Martuza *et al.* (U.S. Patent No. 5,585,096) taken with Roth (U.S. Patent No. 5,747,469), Huber *et al.* (EP 0 415 731), Burton *et al.* (U.S. Patent No.

5,416,017), Smith *et al.* (*Human Gene Ther. 5*:29-35 (1994)), Abe *et al.* (*Proc. Natl. Acad. Sci 90*:282-286 (1993)), Grooteclaes *et al.*, (*Cancer Res. 54*:4193-4199 (1994)), Kovarik *et al.* (*J. Biol. Chem. 268*:9917-9926 (1993)) and Max-Audit, I. *et al.* (*J. Biol. Chem. 268*:5431-5437 (1993)). Applicants respectfully traverse this rejection.

Claims 4, 5, 13, 14, 23, 24, 34 and 35 were canceled in the Amendment and Reply under 37 C.F.R. § 1.111 filed October 13, 1998. Claims 9-12, 17 and18 are canceled in the present amendment. In addition, in an effort to expedite the allowance of the present application, the limitations of claims 7, 26 and 37 have been added to claims 1, 19 and 30, respectively. Since claims 7, 26 and 37 are not part of the present rejection, claims 1, 19 and 30, and the claims which depend therefrom (2, 3, 8, 20-22, 27-33 and 38-40) should be allowable.

Applicants submits that the prior art cited by the Examiner does not teach or suggest the invention defined by claims 1-3, 8, 19-22, 27-33, 38-40, 43 and 44.

Martuza *et al.* teach herpes simplex virus (HSV) vectors that may be used for killing malignant brain tumor cells. No other vector constructs, and most particularly no adenoviral vector constructs, are disclosed, suggested or contemplated by Martuza *et al.* Moreover, Martuza *et al.* make no mention of the E1a, E1b, E2 and E4 coding regions of adenovirus. Therefore, Martuza *et al.* cannot and do not render obvious the presently claimed adenoviral vectors constructs and cells containing such constructs.

Roth does not cure the deficiencies of Martuza *et al.* Roth does teach recombinant adenovirus constructs and the use thereof in combination with a DNA damaging agent or factor to kill cells, in particular, tumor cells. The Roth adenoviral constructs express a tumor

suppressor gene such as p53. Roth also teach adenoviral constructs where the p53 gene is substituted for one of the E1a, E1b, E2 and E4 genes:

> The p53 gene or cDNA may be introduced into a recombinant adenovirus in accordance with the invention simply by inserting or adding the p53 coding sequence into a viral genome. However, the preferred adenoviruses will be replication defective viruses in which a viral gene essential for replication and/or packaging has been deleted from the adenoviral vector construct, allowing the p53 expression region to be introduced in its place. Any gene, whether essential (e.g., E1A, E1B, E2 and E4) or non-essential (e.g., E3) for replication, may be deleted and replaced with p53. Particularly preferred are those vectors and virions in which the E1A and E1B regions of the adenovirus vector have been deleted and the p53 expression region introduced in [its] place, as exemplified by the genome structure of FIG. 1.

Roth at col. 6, line 56, though col. 7, line 3.

Thus, Roth teaches substituting the p53 gene for one of the E1a, E1b, E2 and E4 genes of an adenovirus. Such adenoviral constructs are *replication defective* as one of the essential E1a, E1b, E2 or E4 genes have been deleted. Roth takes advantage of the tumor suppressing properties of p53 in the disclosed constructs to assist the killing of cells. Roth does not teach or suggest the operable linkage of a tissue specific promoter to one of the E1a, E1b, E2 and E4 regions to give a replication conditional vector. The claimed adenoviral constructs function to kill tumor cells by tissue specific *replication* in those cells. Thus, the Roth adenoviral constructs function in a fundamentally different way compared to the claimed adenoviral constructs.

In order to obtain the claimed adenoviral constructs, one of ordinary skill in the art would have to proceed contrary to the express teachings of Roth. This is strong evidence of the nonobviousness of the claimed invention.

The remaining references do not cure the deficiencies of Martuza *et al.* and Roth. These references are cited by the examiner as merely teaching the existence of tissue specific promoters. Therefore, the combination of the references does not teach or suggest Applicants' invention.

Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness. In light of the amendments and remarks above, Applicants respectfully request that the Examiner withdraw the rejection to the claims under 35 U.S.C. § 103(a).

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant(s) therefore respectfully request(s) that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. It is believed that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment is respectfully requested.

Respectfully submitted,

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